Docket No.: 217637US0CONT

IN THE UNITED STATES PATENT & TRADEMARK OFFICE

IN RE APPLICATION OF:

Yusuke AMINO, ET AL. : EXAMINER: ZUCKER

SERIAL NO.: 10/091,500 :

FILED: MARCH 7, 2002 : GROUP ART UNIT: 1621

FOR: METHOD FOR PRODUCING ASPARTAME DERIVATIVE, METHOD FOR PURIFYING THE SAME, CRYSTALS THEREOF AND USES OF THE SAME

DECLARATION OF PROFESSOR JERRY ATWOOD

COMMISSIONER FOR PATENTS
P.O. BOX 1450
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SIR:

Now comes Professor Jerry Atwood, who declares and states:

1. I reside at 5704 Short Line Dr., Columbia, Missouri 65203. I hold a B.S. degree in Chemistry and Mathematics from Southwest Missouri State University (1964) and a Ph.D. in Chemistry from the University of Illinois (1968).

2. Since 1994, I have been employed as Professor and Chairman of the Department of Chemistry at the University of Missouri-Columbia. From 1968 to 1994, I was employed by the University of Alabama, where I successively held the titles of Assistant Professor, Associate Professor, Professor, and University Research Professor. In 1999 I became Curators' Professor at the University of Missouri-Columbia.

3. From 1985 to 1998, I was Editor of the *Journal of Chemical Crystallography*. In 1999 I was named Consulting Editor for the *Journal of Chemical Crystallography*. I have edited the *Journal of Supramolecular Chemistry* since 2000, and I have been Associate Editor of *Chemical*

Communications since 1996. From 1992 until 2000, I was editor of *Supramolecular Chemistry*. From 1985 to 1993, I was Regional Editor for the *Journal of Coordination Chemistry*. I am co-Editor of the *Inclusion Compounds* book series (five volumes), *Comprehensive Supramolecular Chemistry* (ten volumes) and the *Encyclopedia of Supramolecular Chemistry* (two volumes). I currently serve on the Editorial Boards of *Crystal Growth & Design*, *Crystal Engineering*, the *New Journal of Chemistry*, *Supramolecular Chemistry*, and the *Journal of Coordination Chemistry*. I have published more than 500 articles in refereed journals. I have authored ten patents. I am an expert in the fields of crystal growth, crystal engineering, and polymer chemistry. A copy of my curriculum vitae is attached hereto as Appendix A, which is incorporated into and is part of this declaration. I have consulted widely for industry, particularly in the fields of pharmaceutical chemistry and polymer chemistry.

4. I am being compensated at my regular consulting rate for my time spent in preparing this opinion.

5. At the request of Ajinomoto Co., Inc., the assignee of the above-identified application by virtue of assignment recorded at reel/frame: 012981/0897, I have reviewed:

a. the file history of U.S. Patent Application Serial No. 10/091,500 ("the Application") including the specification and all pending claims, filed on March 7, 2002, entitled "Method For Producing Aspartame Derivative, Method For Purifying The Same, Crystals Thereof And Uses Of The Same";

b. U.S. Patent No. 5,480,668, issued to Nofre et al. (the Nofre '668 Patent);

c. U.S. Patent No. 5,510,508, issued to Claude et al. (the Claude '508 Patent);

d. U.S. Patent No. 6,077,962, issued to Prakash et al. (the Prakash '962 Patent).

I have also reviewed the Office Action issued in the Application and dated March 23, 2003 ("the Office Action") and provide the following comments on the scientific basis therefor.

6. In paragraph 11 of the Office Action, the examiner states: "Compounds are distinguished by their atoms and bonds and not by their method of production. The diffraction peaks are an inherent property of the compound disclosed by Nofre [the '668 Patent]."

7. In paragraph 12 of the Office Action, the examiner states: "The properties of the compound disclosed by Nofre, including crystallinity and diffraction pattern, are considered by the Examiner to be inherent properties of the compound disclosed by Nofre."

8. In paragraph 14 of the Office Action, the examiner states: "The properties of the compound disclosed by Nofre, including crystallinity and diffraction pattern, as discussed above, are considered by the Examiner to be inherent properties of the compound disclosed by Nofre."

9. In the paragraphs that follow, I describe the state of the art with regard to the relationship of compounds with specific atoms and bonds to the crystallization and physical properties of such compounds. I then relate the teachings of the Nofre '668 Patent to the teachings of the Application. In summary, my opinion is that the Application contains new teachings not found in the Nofre '668 Patent.

10. Many organic compounds crystallize in more than one form. That is to say, one given organic compound may crystallize in two or more different forms. These forms are not different in the way in which the atoms of the molecule are connected, but rather in the manner in which the molecules relate to each other in the crystalline state. This behavior is referred to as polymorphism. In 1965, McCrone defined a polymorph as "a solid crystalline phase of a given compound resulting from the possiblility of at least two different arrangements of the molecules of that compound in the solid state" (W. C. McCrone in *Physics and Chemistry of the Organic Solid State*, Vol. 2, (Eds.: D. Fox, M. M. Labes, and A Weissberger), pp. 725-67, Wiley Interscience, New York, 1965).

11. Polymorphs may have very different physical properties such as melting point, dissolution rate, solubility, particle size, and hygroscopicity. One polymorph may be much more useful for a given purpose than is another polymorph, even though, chemically, the molecules are the same.

12. Polymorphs were first discovered by chance. Indeed, even with the substantial effort now being brought to bear to the polymorphism issue, there is no way to predict the existence of polymophism for a given compound, regardless of the information available about the manner in

which the atoms are bonded together in the molecule. The American Chemical Society held a so-called "ProSpectives" course in polymorphism last February, and the second such course is scheduled for February 2004. The advertisement for this 2004 course is given in Exhibit B.

13. While it is not possible to predict polymorphism, once polymorphs have been discovered, it is necessary to describe the methods and conditions of crystallzation which will afford reproducibility. In my opinion, it is not sufficient to simply state that a compound is crystallized from a given solvent. Polymorphs may be obtained even from the same solvent under different crystallization conditions. Therefore, the method by which a particular polymorph may reproducibly be obtained is as novel as the polymorph itself.

14. Aspartame, Aspartame hydrates, and Aspartame derivatives are known to exhibit polymorphism (Leung et al., *Journal of Pharmaceutical Sciences*, Vol. 87, pp. 501-507, 1998). Five crystal modifications of Aspartame are known. Ajinomoto Co., as the result of "intensive investigations to improve the workability [of the crystallization] step in the production" found that cooling aqueous solutions of Aspartame without stirring afforded "bundle-like" crystalline aggregates. These bundles had improved handling characteristics, and a European patent was granted for this process in 1985.

15. In the United States, patents related to polymorphs of important drugs are common. Indeed, it is a rare drug that does not now have polymorphs covered by patents. These patents may cover a given polymorph and/or methods of making a given polymorph.

16. The Application teaches the crystallization of the Aspartame derivative N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester. A detailed description of the conditions of crystallization is given. The resulting crystals are defined in terms of their X-ray powder diffraction (XRPD) pattern. Upon reading the Application, one of ordinary skill in the art would understand how to crystallize N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester, and would further know that the desired crystalline compound had been prepared by performing a standard XRPD study.

17. At best, the Nofre '668 Patent teaches a general synthetic method for the production

of the compounds appearing in Table 1. In fact, the only synthetic method exemplified in the Nofre '668 Patent is for N-[N-(3,3-dimethylbutyl)-L-α-aspartyl]-L-phenylalanine 1-methyl ester as at col. 7, l. 47-51, one finds:

> "The gummy precipitate formed is filtered off, dried under vacuum and recrystallized from an ethanol/water mixture (1/1) or from acetonitrile to give 9 g (yield 62%) of N-[N-(3,3-dimethylbutyl)-L-α-aspartyl]-L-phenylalanine 1-methyl ester."

Therefore, not only does the Nofre '668 Patent fail to disclose an actual synthetic method for the N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester compound, it also falls short of the mark with regard to crystallization.

18. In the Application, Example 1, p. 31, l. 15-25, p. 32, l. 1-9, one finds the following teaching:

> "After the reaction solution was concentrated under reduced pressure, the residue was dissolved in 50 ml of ethyl acetate, and moreover, 5 ml of methanol was added to the mixture. When the mixture was allowed to stand, crystals of N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester were precipitated therefrom. The crystals were collected by filtering, washed with a small amount of ethyl acetate and dried under reduced pressure. After these crystals were dissolved in 20 ml of methanol, the mixture was concentrated to half as much. The crystallization proceeded from the oil-like part as 20 ml of water was added gradually to the remaining residue (mixture thus concentrated). The crystals thus precipitated and separated therefrom were filtered after breaking-up and the product was washed with a small amount of mixed solvent of methanol and water, and the product was dried under reduced pressure to obtain 5.76 g (12.6 mmol) of the title compound. When the compound was analyzed by HPLC, the purity of the same was not less than 99%.
>
> Above mother liquor obtained by recrystallization with ethyl acetate-methanol was extracted with water 50 ml twice, and successively the aqueous layer obtained was concentrated under reduced pressure. Similar to the above, the remaining residue was

crystallized from methanol-water, and 0.48 g (1.05 mmol) of the title of object compound were obtained. When the compound was determined by HPLC, the purity of the same was not less than 99%."

19. In this example of the Application, the use of methanol/water is taught, along with sufficient detail to allow one of ordinary skill in the art to obtain the crystalline compound. Further, in Figure 1 of the Application the XRPD of the crystalline compound is presented. This would allow one of ordinary skill in the art to compare his/her XRPD and understand that he/she is practicing the art of the Application.

20. In summary, the teachings of the Nofre '668 Patent at best provides a synthetic method for the production of the N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L-α-asparty]-L-phenylalanine 1-methyl ester molecule, but the crystallization teaching is lacking. Nofre does not teach any crystal form of N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L-α-asparty]-L-phenylalanine 1-methyl ester. Therefore, based on the teaching of the Nofre '668 Patent, one of ordinary skill in the art would not find crystallization and the crystal form of N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L-α-asparty]-L-phenylalanine 1-methyl ester to be obvious. It is only the Application that teaches crystallization and the crystal form of N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L-α-asparty]-L-phenylalanine 1-methyl ester.

21. I declare further that all statements made of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this application or any patent issuing thereon.

22. Further Declarant saith not.

Jerry D Atwood

Jerry Atwood, Ph.D.

September 21, 2003

Date September 21, 2003